REMARKS

Responsive to the Office Action mailed 23 March 2006 and with an extension of time of three months, the present paper is timely filed on or before September 23, 2006.

By the present paper, claim 1 is amended and no claims are cancelled. Accordingly, claims 1 - 36 are in the Application. Entry of the Amendments and reconsideration of the Application are respectfully requested.

Amendments to the Claims:

Claim 1 is amended to recite that the combination is provided in a single crystallization vessel. Support for the amendment can be found in the specification at, for example, page 6, lines 4 - 6, and in the working examples. Applicants respectfully submit that the claim amendments do not introduce new matter into the Application.

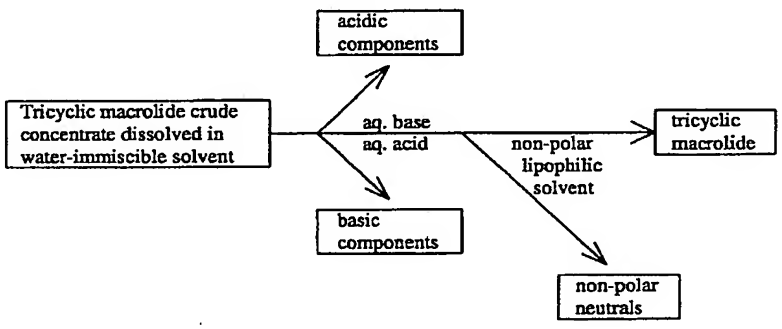
Claim Rejections Under 35 U.S.C. § 103:

Claims 1 - 5, 7 - 13, 15, - 19, 21 - 27, 35, and 36 were rejected as allegedly obvious over United States Patent 5,508,398 (the '398 patent). As Applicants best understand the rejection, the Office rejects the claims as *prima facie* obvious or, in the alternative, as inherently anticipated under 35 U.S.C. § 102 by the '398 patent[1]. Applicants respond accordingly.

Because the '398 patent does not suggest, let alone expressly or inherently teach, all of the limitations of Applicants' claims, arranged as Applicants arrange them, Applicants respectfully traverse.

The '398 patent teaches an extractive method for recovering or separating a macrolide. The process can be represented schematically as follows:

Scheme 1.



"Water-immiscible solvents" are disclosed in the '398 patent at 4:46 to 4:52 and include ethyl acetate and toluene. Both of these solvents are "polar solvents" within the meaning of Applicants' claim 1 (*see* pg. 4, ll. 5 - 9). As pointed-out in the Office Action, an "aqueous" base or "aqueous" acid as used in the first *extraction step*[2] of the method of the '398 patent would introduce water as called for by claim 1. Applicants assume, *arguendo*, that a second phase might form. But the bulk of any such aqueous phase is separated in the process of the '398 patent, leaving behind whatever trace of water as might have dissolved in the water-immiscible solvent. In the case of EtOAc solvent, this could amount to 5 - 10% water. Claim 1 is not limited to any specific ratio of polar solvent : hydrocarbon solvent : water, so any ratio would meet the limitation of the claim.

However, the "extraction" method of the '398 patent[3] is plainly carried-out in at least two distinct steps: extraction of a solution in a water-immiscible solvent with and acid or a base, followed by separation of the phases[4], and optionally, a third step extraction with a non-polar lipophilic solvent. The '398 patent neither teaches nor suggests that a macrolide can be obtained in crystalline form by combining four elements in a single crystallization vessel: a macrolide starting material, a polar solvent, a hydrocarbon solvent, and water, whereby a water-rich phase of pH > 7 is obtained. Because the '398 patent does not teach or suggest all of the limitations of Applicants' claims 1 - 5, 7 - 13, 15, - 19, 21 - 27, 35, and 36 arranged as Applicants have arranged them, Applicants respectfully submit that the rejection is improper and should be withdrawn.

Claims 6, 20, 29 to 32, and 34 were rejected as prima facie obvious over the '398 patent because, as Applicants best understand the rejection, it is alleged that the

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[1] Applicants regret that they do not find, expressly or implicitly, the factual inquiry required by *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Applicants note that, at page 3, the Office Action states that two phases would be "inherent".

[2] The '398 describes extraction as plainly involving physical separation of phases,. *See* '398 patent at 3:67 to 4:6. After a phase is "separated", it is no longer considered present. At column 3, line 4, he '398 patent describes extraction (emphasis added): "[t]he term extraction refers to the procedure of thoroughly mixing a first solution or solvent with a second solution or solvent, immiscible with said first solution or solvent, allowing the immiscible solutions to separate one from the other and physically removing one layer or phase from the other wherein a component in one solution is transferred to the other solution or solvent.

[3] The instant process is a selective crystallization method. To perform a selective crystallization the multiple-phase mixture preferably stands for a contacting time. The resulting solvent phase and water phase dissolve slightly the macrolide , as mother liquor of any crystallization . The '398 patent mentions "extraction" of a solution . See 1/a of '398 . A U which dissolves the macrolide is applied.

[4] See footnote 2.

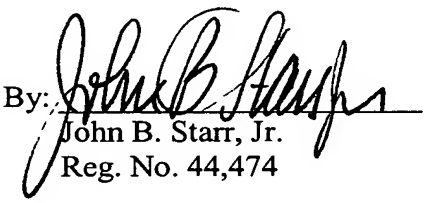
limitations to particular ranges for the process variables are the product of routine process optimization. But the multi-step extraction process of the '398 patent is not Applicants' inventive "one-pot" crystallization method. Because the process disclosed in the '398 patent is fundamentally different from Applicants' inventive process, Applicants respectfully submit that there is no technical basis for the Office's position that optimization of one process is tantamount to optimazation of the other. Accordingly, Applicants respectfully submit that the rejection should be withdrawn.

Claims 14, 28, and 33 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '398 patent in view of Navarro, WO 2000/33878 (WO '878). Because neither the '398 patent nor WO '878, alone or in any combination, teach all of the elements of Applicants' claims, arranged as Applicants have arranged them, Applicants respectfully traverse.

WO '878 teaches means of stabilizing a macrolide and, at page 5, also discloses that rapamycin can be crystalline. But beyond disclosing that, as Applicants agree, rapamycin - a macrolide - can be crystalline, WO '88 adds nothing to the process of the '398 patent. Knowing that rapamycin can be crystalline and knowing, as a rule-of-thumb, that crystalline materials are easier to handle than, e.g., oils or gums, the skilled artisan of the day *would have been motivated to try* to obtain any macrolide as a crystalline material. Merely knowing that rapamycin can be crystalline would not have taught or suggested to the skilled artisan that they modify the multi-step extraction process of the '398 patent to arrive at Applicants' inventive one-pot process. Accordingly, Applicants respectfully submit that the rejection is improper and should be withdrawn.

Respectfully submitted,

Date: September 22, 2006

By: 
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